



Letter to the Editor

Reply to Letter to the Editor: "Refining the evidence linking dietary diversity, genetic susceptibility, and dementia"



Dear Editor,

We appreciate Hongye Yao and colleagues for their commentary on our recently published article "Association of dietary diversity, genetic susceptibility, and the risk of incident dementia: A prospective cohort study" [1]. They have provided pertinent insights and raised important considerations regarding our work, for which we offer the following responses for further discussion.

Our study employed Cox proportional hazards models to assess the association between dietary diversity score (DDS) and incident dementia. Although some studies on dementia have performed competing risk models, it is important to note that these studies have primarily enrolled older adults [2]. This is because the underlying premise for using competing risk models is that a competing event effectively prevents the occurrence of the primary event of interest. Studies that focus on dementia often observe competing risks due to death in older populations with elevated mortality rates. For example, Chang et al. [2] compared Cox proportional hazards models with competing risk models that treat death as a competing event to evaluate the association between smoking and Alzheimer's disease (AD). They found that among individuals aged 65 to 74, the two models gave very similar hazard ratio (HR) estimates. In contrast, among those aged 75 and older, failure to account for the competing risk of death resulted in biased estimates, with the Cox model exhibiting a stronger "protective" effect for smoking than the competing risks model. However, our study used the UK Biobank cohort, in which participants were mostly middle-aged, with a mean age of 56.25 years. Given the low risk of death in this cohort, the impact of death as a competing event on the primary outcome of dementia is minimal. Consequently, the association between DDS and incident dementia as estimated with the Cox model is reliable.

Our study aimed to investigate the association between DDS and incident dementia. We acknowledge that the UK Biobank exhibits a "healthy volunteer" selection bias. However, in studies that include a sufficiently large and diverse sample of individuals with varying levels of exposure and strong internal validity, this bias should not be regarded as a limitation in producing generalizable associations of exposures with disease, as it tends to influence all exposure groups similarly. Multiple studies have demonstrated that the large sample size and diverse range of exposure measures in the UK Biobank enable robust inferences regarding the associations between exposures and health outcomes that are generalizable to other populations [3]. The protective effect of higher dietary diversity on dementia observed in our study has also been validated in other representative population cohorts, further confirming the reliability of this association [4].

Our published study focused on the influence of dietary diversity and genetic predisposition on the onset of dementia. Hongye Yao and colleagues have proposed a promising topic for future investigations by suggesting that peripheral biomarkers—such as phosphorylated tau (P-tau), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP)—be utilized as intermediate phenotypes to delineate the trajectory of dementia. Peripheral biomarkers offer unique advantages in detecting subclinical neuroinflammation and irreversible neuronal damage, thereby demonstrating potential as early diagnostic tools for AD and dementia [5]. Future research should further incorporate biomarker measurements to examine the potential of dietary interventions in influencing pathological changes and disease progression in dementia.

We thank Hongye Yao and colleagues for their interest and comments and appreciate the journal's opportunity to engage in this dialogue, as we look forward to continued research in this promising area.

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None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Boyue Zhao: Conceptualization, Writing – original draft. **Feng Zhang:** Conceptualization, Writing – review & editing.

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